REMARKS

Claims 1, 20-24, 45, 57-59, 61, 62, 67, and 77 are pending.

Claim 23 has been cancelled herein without prejudice.

Applicants thank the Examiner for withdrawal of the prior rejections as stated in the present Office Action.

Applicants acknowledge the Examiner's new and maintained grounds of rejection as addressed herein.

Applicants have responsively amended claims 1, 20, 21, 22, 24, 59, 61, 62 and 77, and have provided supportive additional comments and arguments in view of same.

Applicants respectfully contend that the presently amended claims are allowable.

Rejections under 35 U.S.C. § 112, second paragraph

The Examiner has rejected claims 1, 20-24, 45, 57-59, 61, 62, 67, and 77, under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for reasons as stated in the Office Action (e.g., recitation of "consisting of essentially" instead of "consisting essentially of").

Applicants thank the Examiner for pointing out this inadvertent error, and have responsively amended the claims to obviate these rejections, and therefore respectfully request withdrawal of these rejections. No new matter has been added

Rejections under 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 1, 20-24, 45, 57-59, 61, 62, 67, and 77, under 35 U.S.C. § 112, first paragraph, in view of alleged new matter.

Specifically, the Examiner states that "the specification as originally filed does not appear to provide support for the amendment to the claims to recite that hypomethylation of PITX2 is indicative of low risk for relapse and that hypermethylation of PITX is indicative of high risk for relapse" (Office Action at page 5). The Examiner states that while the description of Figure 19 indicates "that the upper dotted line shows responders and the lower unbroken line shows non-

responders," "Figure 19 does not provide any information to indicate the hypomethylation or hypermethylation status of the responders or non-responders." Finally, the Examiner states that while "this figure provides information regarding only time of disease-free survival. This is not equivalent to teaching that hypomethylation is correlated with low risk of relapse and that hypermethylation is correlated with high risk of relapse" (Office Action at page 5).

Applicants respectfully traverse this rejection, based on the teachings of the specification at Figure 19, Figure 5 and Example 1 at page 59, last paragraph.

As an initial matter, Applicants' rebuttal at page 10 of Applicants' last Response inadvertently recited page 58 instead of the intended page 45, and Applicants apologize for any confusion thus created.

Support for recitation that hypomethylation is correlated with low risk of relapse and that hypermethylation is correlated with high risk of relapse is found throughout the originally filed specification, and particularly in Figure 19, in combination with the data set and Table on pages 44-45, and in combination with Figure 5. Specifically, Figure 19 shows Kaplan-Meier curves of estimated disease free survival wherein the population of analyzed patients was split into two equal sized groups by their PITX2 methylation (p59 last paragraph). The survival of patients over time is displayed. The upper dotted line (responders) is identified in the insert as "-" (hypomethylated), and the lower solid line (non-responders) is identified in the insert as "+" (hypermethylated). As would be evident to one of ordinary skill in the art, therefore, hypomethylation ("-") is indicative of responders, while hypermethylation ("+") is indicative of non-responders. More patients with hypomethylated PITX2 are alive at a certain time point than patients with hypermethylated PITX2. In other words, patients having hypomethylated PITX2 have a lower risk for relapse (i.e. responders) than patients having hypermethylated PITX2 (high risk of relapse i.e. non-responders). This is also evident for a person skilled in the relevant art in view of the section "Data set 2: Adjuvant setting" of Example 1, wherein the results of the Cox model are specified (see specification at pages 44 and 45). As will be immediately evident to one of skill in the art, the positive value of the specified coefficient (coef) of the Cox model for PITX2

indicates that an increased risk for relapse correlates with hypermethylation of PITX2.

Entirely consistent with Figure 19, the methylation matrix of Figure 5 shows the methylation of respective genes for different individuals, where with respect to PITX2, non-responders are on average more methylated than responders, indicating that the average non-responder is hypermethylated while the average responder is hypomethylated.

Applicants, therefore, respectfully request withdrawal of this rejection.

Rejections under 35 U.S.C. § 112, first paragraph

The Examiner has maintained the rejection of claims 1, 20-24, 45, 57-59, 61, 62, 67, and 77, under 35 U.S.C. § 112, first paragraph, as allegedly lacking sufficient enablement.

The Examiner states that the rejection is maintained for reasons of record.

As an initial matter, claims 62, 67 and 77 have been limited to human subjects. Specifically, claims 45 and 62 are limited to human subjects, and claims 67 and 77 depend from claims 62, and 45 and 62, respectively.

First, following the comments in the above "new matter" rejection, the Examiner questions whether the Example 1, Data set 2 (adjuvant therapy) data (coefficient of the Cox model for PITX2) supports the claimed correlation between PITX2 methylation status and response to therapeutic treatment. In this regard, the Examiner further comments (at page 7) on the fact that the claims are not limited to Adjuvant therapy, while data of Example 1, Data set 2, appears to be so limited, and that that the number of patients treated, and the type of treatment, sex of patient, etc., is not given.

Applicants have amended claims 1, 45 and 62 to recite "adjuvant therapeutic treatment" in place of therapeutic treatment." Additionally, Applicants point out that the specification at page 40 discloses that the number of analyzed patients is specified with 200. Moreover, the application refers to breast cancer or breast proliferative disorders, and as will be appreciated in the art, the analyzed patients are human females.

Second, the Examiner (at page 8 of the Office Action) states that she does not accept our

prior argument relating to the teachings of Sorlie (2001) and Perou (2001), because our claims recite "breast tissue proliferative disorder," rather than "breast cancer," and because Sorlie (2001) and Perou (2001) teach unpredictability with respect to correlating breast cancer types with gene expression. The Examiner states that gene expression patterns can reflect methylation differences, and thus the Examiner urges that Sorlie (2001) and Perou (2001) teach unpredictability of correlating methylation differences with all types of breast cancer.

Applicants have, in this respect, additionally amended claims 1, 45 and 62 to recite "estrogen receptor-positive breast cancer" in place of "a breast tissue cell proliferative disorder," and conforming amendments have been made to claims 2, 21, 22 and 24. Claim 23 has been deleted without prejudice. Additionally, with respect to the teachings of Sorlie (2001), Perou (2001), Martens (2005) and Nimmrich (2008), Applicants reaffirm and reassert Applicants' rebuttal arguments of record. The Examiner has shown no basis for the Examiner's extrapolation of "that gene expression patterns *can* reflect methylation differences" as being relevant. Applicants Disclosure. With regard to the permissible scope of the breast tissue proliferative disorder genus, it is well recognized in the art that (1) a subclassification of breast cancer tissue into breast tissue subtypes is irrelevant for clinical implications (see attached literature citations to Sorlie et al., *PNAS*, 98:10869-10874, 2001, and Perou et al., *Nature* 406:747-752, 2000); and (2) all cells of the breast tissue originate from a common precursor. Moreover independent claims 1, 45 and 62 are already limited to a subclass of breast cancer namely estrogen receptor-positive cells. With regard to the mutually contradictory results between Martens et al., and Nimmrich et al., Applicants point out that Martens et al., was not in the adjuvant setting, and thus respectfully maintain that the Examiner has not presented any reasonably basis why these two *post-filing* references should preclude patentability of the presently amended claims, which are supported by Applicants' specification. A

Third, Applicants contend that there is no logical support for the Examiner's statement that "the specification does not teach that survival time is a measure of the risk of relapse. One of ordinary skill in the art will appreciate that there is a correlation between risk of relapse and

survival time, because the higher the risk for relapse, that greater the frequency of relapse and the shorter the survival.

Fourth, the Examiner (at pages 10 and 11) additionally raises issues with respect to the definition of "complementary" sequences, and urges that the specification does not define that "complementary" sequences mean full (100%) complementarity. Applicants respectfully contend that, unless stated otherwise, complementarity, as recognized and construed in the art, refers to complete complementarity. Applicants, have nonetheless amended the claims to obviate this rejection by reciting "complements thereof," rather than "sequences complementary thereto." Applicants contend the term "complement" is just that, "the complement".

Fifth, the Examiner remarks that the work "contiguous' could be construed to include any sequences that are any distance upstream or downstream of the recited sequences. Applicants point out however, that Applicants' claims do not merely recite "contiguous" but rather recite "contiguous portions thereof" which clarifies that the contiguous sequence portions are within the recited sequences, and not, as urged by the Examiner—any distance upstream or downstream of the recited sequences.

Sixth, with respect to the Examiner's arguments of record with respect to any alleged requirement for undue experimentation, Applicants respectfully request withdrawal of this rejection based on the present limiting claim amendments, and in view of Applicants' rebuttal remarks already of record with respect to the availability of high-throughput methylation assays, and the nature of co-methylation that occurs within the PITX2 gene and its regulatory sequences, Applicants contend that while Applicants' specification and working Examples do not explicitly include analysis of each and every CpG position within the PITX2 gene and/or its regulatory elements, Applicants' method claims are nonetheless entitled to a broad scope with respect to the PITX2 gene limitation. A contrary conclusion would not comport with U.S. patent law on enablement.

Specifically, to satisfy the enablement requirement of 35 U.S.C. §112, first paragraph, the specification must teach one of skill in the art to make and use the invention without *undue*

experimentation (*Atlas Powder Co.*), where this requirement can be satisfied by providing sufficient disclosure, either through illustrative examples or terminology, to teach one of skill in the art how to make and how to use the claimed subject matter without undue experimentation. This clause does not require "a specific example of everything within the scope of a broad claim" (*In re Anderson*). A patentee is not only entitled to narrow claims particularly directed to the preferred embodiment, but also to broad claims which define the invention without a reference to specific instrumentalities (*Id*). Further, because "it is manifestly impracticable for an applicant who discloses a generic invention to give an example of every species falling within it, or even to name every such species, it is sufficient if the disclosure teaches those skilled in the art what the invention is and how to practice it" (*In re Grimme*). There is, therefore, no requirement for disclosure of every species within a genus. Applicants are entitled to claims that are commensurate in scope not only with what Applicants have specifically exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which the Applicants have disclosed.

Applicants point out that under U.S. patent law, a considerable amount of experimentation is permissible, particularly if it is routine experimentation. As appreciated by the Examiner, the amount of experimentation that is permissible depends upon a number of factors (A, claim scope; B, nature of invention; C, state of the prior art; D, level of skill in the art; E, level of predictability; F, amount of direction provided; G, working examples; and H, quantity of experimentation required) as discussed herein above. The Examiner has offered insufficient evidence to support that any alleged amount of experimentation is other than rapid, high-throughput and routine.

With respect to these factors in the present case, the Examiner appreciates that the level of skill in the art is very high (as evidenced by the Examiner's own cited art references), and given the nature of the invention in terms of the realities of high-throughput methylation assays and co-methylation within the PITX2 gene and its regulatory sequences, Applicants contend that a *prima facie* case of insufficient enablement cannot reasonably be supported under U.S. Patent law, because under the proper analysis of *all* Wands factors, any amount of experimentation required to

practice the invention as presently claimed would in fact be merely routine, and insufficient to support the Examiner's allegation of *undue* experimentation. Improper limitation of Applicants' invention to particular exemplary preferred regions within the PITX2 gene is not only impermissible under U.S. patent law in view of the present facts, but would also be unjustifiable—in that a person of ordinary skill in the art could, using routine, efficient methods readily identify and select alternate diagnostic CpG positions within the PITX2 gene and its regulatory sequences but outside Applicants' exemplary preferred regions, thus effectively eviscerating Applicants' claimed invention.

Applicants are entitled to claims that are commensurate in scope not only with what Applicants have specifically exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which the Applicants have disclosed.

In view of the present claim amendments, Applicants respectfully contend that the currently amended claim scope is commensurate with the teachings of the specification, and request withdrawal of the Examiner's rejection based on lack of sufficient enablement.

Obviousness-type Double Patenting Rejection

The Examiner has *provisionally* rejected claims 1, 20-24, 45, 57-59, 61, 62, 67, and 77, on the grounds of nonstatutory obviousness-type double patenting, as being unpatentable over claims 1, 3-6, 8-11, and 20-21 of Applicants' copending Application No. 10/582,705.

Applicants respectfully traverse this rejection based on the fact that in view of the prior art (including that specifically cited and discussed by the Examiner in the present Office Action), no *prima facie* case of obviousness can be supported.

Specifically, Applicants have herein amended the claims, as discussed above, to recite "complements thereof," in place of "sequences complementary thereto," such that the Examiner's reliance on "complementarity" to SEQ ID NO:23 of '705 is not reasonably supported.

Additionally, the pending application claims PITX2 as a treatment response predictive marker, whereas Applicants' Serial No. 10/582,705 ('078US0, P190US) claims PITX2 as prognositic marker, such that the two application claim distinct inventions.

In view of the present claim amendments and arguments, Applicants respectfully request withdrawal of this provisional rejection.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully request entry of the present Response and Amendment and allowance of all claims as provided herein above. The Examiner is encouraged to phone Applicants' attorney, Barry L. Davison, to resolve any outstanding issues and expedite allowance of this application.

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